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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): Glen H. ERIKSON et al.

Serial No: 09/713,177 Group Art Unit: 1637

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Att. Docket No.: E1047/20048 Confirmation No.: 3217

For: TRIPLEX AND QUADRUPLEX CATALYTIC HYBRIDIZATION

REQUEST FOR RECONSIDERATION AFTER FINAL REJECTION

Box AF
Commissioner for Patents
Washington, DC 20231

Sir:

In response to the Final Rejection dated June 5, 2002, favorable reconsideration is respectfully requested in view of the following remarks.

Claims 1-63 are pending.

Applicants gratefully acknowledge the withdrawal of all the prior art related rejections.

Claims 1-63 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing non-enabled subject matter. This rejection is respectfully traversed.

An invention is patentably enabled if one of ordinary skill in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. See, e.g., MPEP § 2164.01 *citing* United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The first step in an enablement analysis is to construe the claims. MPEP § 2164. Composition claim 1 specifies a catalytic hybridization composition comprising a probe, an enzyme, a target and a hybridization medium, wherein at least one of the probe and the target is double-stranded and is bonded to the other of the probe or the target solely through Watson-Crick base triplets. Method claim 24 specifies a catalytic hybridization method for assaying binding, comprising the formation of probe-target multiplexes like those in claim 1. The meaning of Watson-Crick base triplets in the context of the invention is provided in the specification at page 12, lines 17-22:

> In certain triplex and quadruplex embodiments, each nucleobase binds to no more than two other nucleobases. Thus, in addition to the traditional Watson-Crick base pairs, such embodiments include the following Watson-Crick base triplets: A-T-A, T-A-T, U-A-T, T-A-U, A-U-A, U-A-U, G-C-G and/or C-G-C (including C+-G-C, and/or any other ionized species of base).

in view of the following passage of the application at page 11, lines 17-24:

> As used herein, the term "Watson-Crick bonding" is intended to define specific association between opposing pairs of nucleic acid (and/or nucleic acid analogue) strands via matched, opposing bases. While the formation of a Watson-Crick quadruplex may sometimes be referred to as a hybridization event herein, that is merely for convenience and is not intended to limit the scope of the invention with respect to how the formation of a Watson-Crick quadruplex can be best characterized.

One of ordinary skill in the art would have understood from the foregoing that the probe-target multiplexes of claims 1 and 24 are triplexes of three nucleobase-containing strands and quadruplexes of four nucleobase-containing strands, wherein Adenines align with Thymines (or Uracils) and Cytosines align with Guanines. Although the original disclosure does not explicitly disclose the interatom hydrogen bond locations, distances and quantities like those of duplex DNA figure in the Final Rejection at page 5, such additional information is not necessary to "make or use" the claimed invention, which does not specify such nanoscale features of the invention. The working examples of the parent 09/664,827 application show that Applicants were able to make and use Watson-Crick multiplexes without undertaking detailed biophysical studies. See the attached Rule 132 Declaration of Dr. J. Hans van de Sande (hereinafter the "JHS Declaration") at, e.g., paragraph 7. Likewise, one of ordinary skill in the art (whom the Final Rejection acknowledges has a high level of skill) would be able to make and use with no more than routine experimentation the claimed multiplexes for purposes such as the claimed assay without ever knowing for certain the location, length and/or number of hydrogen bonds between adjacent bases in the multiplex. See the JHS Declaration at, e.g., paragraph 10.

Applicants have shown specific association of non-denatured dsDNA targets with non-denatured dsDNA probes. The targets and probes align Adenine to Thymine (or Uracil) and Cytosine to Guanine. In light of Applicants' evidence that two strands on opposing non-denatured duplexes specifically interact together A:T(U) and C:G, one of ordinary skill in the art would have found it reasonable to infer that adjacent bases in the remaining two strands of the duplexes would be brought into close enough proximity by the initial pairing of opposing strands to specifically interact together A:T(U) and C:G. JHS Declaration at paragraphs 8-9. This inference would not have been considered by an ordinarily skilled artisan to be a direct affront to the conventional understanding of Watson-Crick bonding, so much as a reasonable corollary of the paradigm-shifting evidence of specific binding between non-denatured duplexes of mixed bases. JHS Declaration at paragraphs 8-9. See also the inventors' U.S. Patents Nos. 6,420,115 to Erikson et al., 6,403,313 to Daksis et al. and 6,265,170 to Picard et al., each of which provides additional evidence (in the form of Watson-Crick triplex binding studies) that the conventional understanding of Watson-Crick bonding is incomplete and should not be accorded the stature of an immutable truth in evaluating the enablement and credible utility of this invention. Thus, the high level of evidence being required

by the Patent Office for this invention is directly met by the binding studies of the parent applications (including 09/664,827), which show non-denatured Watson-Crick triplex and quadruplex binding complexes, and Applicants should not be required to make an additional or equally burdensome showing regarding additional details irrelevant to making or using the invention.

Furthermore, Professor van de Sande cites an article (attached to his Declaration as Exhibit B) published subsequent to the filing of this application, which disproves the theory in the Final Rejection at page 6, last sentence, that "Watson-crick hydrogen bonding surfaces are inaccessible for any other strands [i.e., strands other than the two hybridized strands of conventional duplexes] since two strands are already interacting with each other at the center of the double helix." Zhang et al., "Dimeric DNA Quadruplex Containing Major Groove Aligned A•T•A•T and G•C•G•C Tetrads Stabilized by Inter-subunit Watson-Crick A•T and G•C Pairs," 312 J. Mol. Biol. 1073-88 (Oct. 5, 2001), shows through NMR studies the formation of A-T-A-T tetrads similar to previously discovered G-C-G-C tetrads. Zhang et al. at pages 1073-74 states:

> [E]fforts have been made to identify and characterize G•C•G•C tetrads, where a pair of Watson-Crick G•C pairs can potentially align either through their major groove or their minor groove edges. . . . recent studies have demonstrated that G•C•G•C tetrads aligned through their major groove edges can switch between two distinct alignment geometries

> [shown in Figure 1(a) and 1(b)]. . . . The major groove-aligned G•C•G•C tetrad has now been observed in a range of DNA quadruplexes and appears to be a robust tetrad motif adopted by a wide range of DNA sequences.

Figure 1 of Zhang et al. shows how major groove-aligned G•C•G•C and A•T•A•T tetrads in their direct alignment geometry have each G hydrogen bonded to each C, and each A hydrogen bonded to each T. Thus, contrary to the Final Rejection, Zhang et al. and the art cited therein (whether prior or not) shows that triplex and quadruplex G-C-G-C and A-T-A-T binding is reasonably credible. JHS Declaration at paragraphs 8-9.

In summary, it should be apparent that the claimed invention is patentably enabled when the Wands Factors are properly applied. Contrary to the Final Rejection at page 9, line 7, the high skill level in the art is not the only factor favoring Applicants. Firstly, along with a high level of skill comes a high tolerance of experimental complexity. Secondly, the art does recognize the existence of triplex/quadruplex G-C-G-C and A-T-A-T binding. Thirdly, working examples of such binding are incorporated by reference into the present disclosure from the parent applications. The fact that the Office might prefer working NMR or crystallographic examples is no basis for completely ignoring the evidentiary weight of the extensive binding studies in the application, particularly in view of the JHS Declaration's

explanation of the significance of the binding studies. Moreover, the working examples are much more relevant to "making and using" the claimed invention than the requested biophysical studies, as suggested by the JHS Declaration at paragraph 10.

Accordingly, reconsideration and withdrawal of the non-enablement rejection are respectfully requested.

Claims 1-25 and 50-51 stand rejected under 35 U.S.C. § 101, as allegedly lacking patentable utility. This rejection is respectfully traversed.

The stated basis for this rejection is set forth in the Final Rejection at page 9, last line, to page 10, line 3, as follows:

> [T]he basic multiplex structure involving Watson-Crick base pairing with more than two strands is incredible and use of such structure is incredible based on unpredictability of the multiplex structure involving Watson-Crick pairing with more than two strands, as discussed above in the enablement rejection.

According to MPEP § 2107.02:

> To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a prima facie showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the prima facie showing. In re Gaubert, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975).

The Final Rejection fails to make a *prima facie* showing under 35 U.S.C. § 101, because the factual assumptions underlying the

purported showing are incorrect and incomplete, as shown above with respect to the non-enablement rejection.

Working examples are incorporated by reference into the specification. If the Office maintains that the working examples do not substantiate the existence of quadruplexes, it should provide "[a]n explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible." MPEP § 2107.02. The Final Rejection does not even attempt to show that the working examples are unreliable or irrelevant to the credible utility of the claimed invention.

It was Supervisory Examiner Fredman's theory at the January 15, 2002 interview that the working examples could merely be an example of strand invasion that has been misinterpreted by the inventors. This theory was refuted by Jasmine Daksis in her Rule 132 Declaration of January 18, 2002. Neither this theory, nor any alternative theory explaining away Applicants' working examples, is suggested in the Final Rejection.

Even if the Office had made a *prima facie* showing, the showing is rebutted by Applicants' showing, including the attached Declaration of Professor van de Sande, wherein the Professor describes through well-reasoned logic and supporting evidence how one of ordinary skill in the art would find the claimed invention

to be reasonably credible. The art recognizes the existence of triplex/quadruplex G-C-G-C and A-T-A-T binding, contrary to the assertion in the Final Rejection.

Accordingly, reconsideration and withdrawal of the utility rejection are respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
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